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UK guideline on the transition and management of childhood liver diseases in adulthood

Deepak Joshi[1] | Jeremy Nayagam[1] | Lisa Clay[2] | Jenny Yerlett[2] | Lee Claridge[3] | Jemma Day[4] | James Ferguson[5] | Paul Mckie[6] | Roshni Vara[2,7] | Henry Pargeter[8] | Rachel Lockyer[8] | Rebecca Jones[3] | Michael Heneghan[1] | Marianne Samyn[2]

[1]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK

[2]Paediatric Liver, GI and Nutrition service, King's College Hospital NHS Foundation Trust, London, UK

[3]Leeds Liver Unit, St James's University Hospital, Leeds, UK

[4]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

[5]National Institute for Health Research, Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK

[6]Department of Social Work, King's College Hospital NHS Foundation Trust, London, UK

[7]Evelina London Children's Hospital, London, UK

[8]Patient Representative, London, UK

Correspondence
Deepak Joshi, Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK.
Email: d.joshi@nhs.net

Summary

Introduction: Improved outcomes of liver disease in childhood and young adulthood have resulted in an increasing number of young adults (YA) entering adult liver services. The adult hepatologist therefore requires a working knowledge in diseases that arise almost exclusively in children and their complications in adulthood.

Aims: To provide adult hepatologists with succinct guidelines on aspects of transitional care in YA relevant to key disease aetiologies encountered in clinical practice.

Methods: A systematic literature search was undertaken using the Pubmed, Medline, Web of Knowledge and Cochrane database from 1980 to 2023. MeSH search terms relating to liver diseases ('cholestatic liver diseases', 'biliary atresia', 'metabolic', 'paediatric liver diseases', 'autoimmune liver diseases'), transition to adult care ('transition services', 'young adult services') and adolescent care were used. The quality of evidence and the grading of recommendations were appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: These guidelines deal with the transition of YA and address key aetiologies for the adult hepatologist under the following headings: (1) Models and provision of care; (2) screening and management of mental health disorders; (3) aetiologies; (4) timing and role of liver transplantation; and (5) sexual health and fertility.

Conclusions: These are the first nationally developed guidelines on the transition and management of childhood liver diseases in adulthood. They provide a framework upon which to base clinical care, which we envisage will lead to improved outcomes for YA with chronic liver disease.

The Handling Editor for this article was Professor Gideon Hirschfield, and this uncomissioned review was accepted for publication after full peer review.

1 | INTRODUCTION

Adolescence is a transitional stage of psychosocial development and a time of rapid physical growth and change. This developmental period includes sexual maturation, rapid cognitive development, emotional changes and the transition from total social and economic dependence to relative independence. Young adults (YA) have different needs than younger children and older adults. Adolescence is a time when lifelong health behaviours are established.[1] Non-adherence to treatment, medical advice and clinic appointments is common in adolescence, although a concern for all those working with YA and often challenging to manage. The World Health Organization acknowledges YA between the ages of 11 and 24 years of age as a distinct population requiring a dedicated healthcare provision tailored to their specific needs.

Improved outcomes of liver disease in childhood and young adulthood have resulted in an increasing number of YA entering adult liver services. The exact number of paediatric patients transitioning into adult care in the UK is unknown but is likely to be in the order of 100–150 per annum. Eight hundred and sixty-seven YA transferred care from the three UK national paediatric liver programmes into adult services between 2008 and 2015, which included post-transplant and chronic liver disease patients.[2]

A position paper from ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) and EASL (European Association for the Study of the Liver) highlighted that in addition to infectious and autoimmune liver diseases, paediatric liver diseases encompass a number of relatively rare conditions, including biliary atresia (BA), metabolic and genetic conditions and sequelae of their treatment.[3] The adult hepatologist therefore requires a working knowledge in diseases that arise almost exclusively in children and their complications in adulthood. This knowledge is not widespread, and the paucity of a formal transition experience presents a barrier to optimal care.[4]

1.1 | Guideline development

The need for a guideline on this topic was highlighted by the Liver section of the British Society of Gastroenterology (BSG). At present, no guidelines exist on the management of paediatric liver diseases for the adult hepatologist. The guideline proposal was reviewed and accepted by the Clinical Services and Standards Committee (CSSC) in 2020. Members of the guideline committee were invited and included a multi-disciplinary approach among adults and paediatric healthcare professionals (HCPs). The draft guideline was submitted for review by the BSG Liver Committee, CSSC and BSG Council and revised in response to their comments.

1.1.1 | Data sources and search strategy

A systematic literature search was undertaken using the Pubmed, Medline, Web of Knowledge and Cochrane database from 1980 to 2023. MeSH search terms relating to liver diseases ('cholestatic liver diseases', 'biliary atresia', 'metabolic', 'paediatric liver diseases', 'autoimmune liver diseases'), transition to adult care ('transition services', 'young adult services') and adolescent care were used. Sections were then divided according to clinical experience and expertise, allowing stakeholders to focus on key publications.

1.2 | Assessing the quality of guidelines: The AGREE II instrument

The AGREE II instrument is an accepted method for appraising clinical guidelines.[5] Six domains are listed:

1.2.1 | Scope and purpose

The guidelines are intended for use by HCPs managing individuals with childhood liver diseases in adult services. The BSG published guidelines on the transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care in 2017,[6] but no specific guidelines are available to help adult clinicians on the management of childhood liver diseases.

1.2.2 | Guideline development group membership and stakeholder involvement

Membership of the group includes hepatologists, specialist nurses, psychologists, social workers and patient representatives. The guideline has been reviewed by BASL (British Association for the Study of the Liver) and BSPGHAN (British Society of Paediatric Gastroenterology, Hepatology and Nutrition).

1.2.3 | Rigour of development

Due to the COVID-19 pandemic, no face-to-face meetings were possible. Regular correspondence was maintained by the chair (D.J.) and the group. Virtual meetings were used.

In accordance with BSG advice on the production of guidelines, the group applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system. The strength of the recommendation was either strong or weak. Where the recommendation was unanimous, a 'strong' recommendation was used, and where the decision was by majority and the recommendation was moderate or weak, 'we suggest' was used. The grading of evidence was based on four level of evidence (high, moderate, low and very low) and the strength of our recommendation (strong, moderate or weak).[6] Topics of disagreement were subject to discussion and, if necessary, voting by members of the guidelines group.

1.2.4 | Clarity and presentation

Recommendations are intended to be specific to diseases and patient groups for HCPs to facilitate the transition process and provide clinical care within a local setting.

1.2.5 | Applicability

Where appropriate, we have reviewed the organisational changes that may be required to apply the recommendations. We have identified key criteria for monitoring and audit opportunities.

1.2.6 | Editorial independence and conflict of interest

All guideline group members have declared no conflicts of interest.

2 | RECOMMENDATIONS

2.1 | Models and provision of care

- We suggest an individualised, multi-disciplinary team approach to YA undergoing transition from paediatric to adult care (Evidence: Moderate; Recommendation: Strong).
- We suggest self-management strategies should be developed with YA and their carer(s)/parent(s) (Moderate, Strong).
- Carer(s)/parent(s) should be encouraged to participate in the transition process (Low, Strong).
- We suggest that the readiness of transfer for YAs not be based solely on age (Low, Strong).

2.2 | Screening and management of mental health disorders

- Mental health should be explored routinely using the HEADSS tool as part of routine clinical practice by a multi-disciplinary team. This can also include the use of standardised screening questionnaires, such as the PHQ-9 and GAD-7 (High, Strong).
- Where embedded psychological support is not available, clinicians should familiarise themselves with onward local pathways for mental health support (High, Strong).
- The impact of psychosocial stressors on young people's adherence to medication/clinic attendance and self-management of their condition should be considered (High, Strong).
- Substance use should be explored routinely with patients as part of routine clinical practice. This can include the use of standardised screening questionnaires, such as the AUDIT-C and DAST (High, Strong).

2.3 | Aetiologies

2.3.1 | Autoimmune liver disease

- Assessment of adherence to treatment using the HEADSS tool should be included in routine clinical settings to avoid relapse of AILD (Low, Strong).
- Cessation of treatment in type 1 autoimmune hepatitis (AIH) should not be considered during puberty and only after a period of both biochemical and histological remission (High, Strong).
- Patients with ASC should be reassessed (imaging, histology and biochemically) for evolution into PSC and the requirement for ongoing immunosuppression (Low, Strong).
- Bone health screening should be undertaken every 2–3 years (Moderate, Moderate).
- Surveillance with ultrasound for hepatocellular carcinoma (HCC) in cirrhotic patients every 6 months (Low, Moderate).

2.3.2 | Biliary atresia

- We suggest YA with BA should be transitioned to an adult liver service with expertise in the management of BA (Low, Strong).
- We suggest that YAs with BA be monitored (6–12 monthly) for cholangitis, the complications of cirrhosis and the complications of portal hypertension (PHT; Low, Strong).

2.3.3 | Progressive familial intrahepatic cholestasis

- We suggest individuals with a diagnosis of PFIC and no genetic variant identified on historical testing should consider repeat genetic sequencing with modern technology (Low, Weak).
- First-degree relatives should be offered genetic counselling and clinical review. The age at which the presence of liver disease should be evaluated is unclear, as heterozygotes can present in later life; therefore, longitudinal follow-up is recommended (High, Strong) UDCA (10–15 mg/kg) should be trialled. In those with no biochemical response, it can be continued in the absence of side effects (Low, Moderate).
- The use of apical sodium bile acid transporter (ASBT) inhibitors is recommended (High, Strong).

2.3.4 | Alagille syndrome

- We recommend referral for genetic counselling when patients with ALGS are planning a family, or when their family members are undergoing genetic testing (High, Strong).
- We suggest that YA with extra-hepatic (cardiac, pulmonary, renal) manifestations of ALGS should be followed up by the relevant specialists with multi-disciplinary working (Moderate, Strong).

- Consideration of treatment with new therapies that is ASBT inhibitors or inclusion in a clinical trial (High, Strong).
- YAs should be managed in specialist centres with early consideration for liver transplantation in those with refractory pruritus and progressive hyperbilirubinaemia (Low, Strong).

2.3.5 | Alpha 1 antitrypsin deficiency

- We suggest that all patients should undergo yearly liver blood tests and liver ultrasound with regular monitoring for the development of liver disease (Moderate, Moderate).
- All patients should be educated on the risks of smoking and receive smoking cessation support (High, Strong).
- Patients should undergo yearly pulmonary spirometry (Moderate, Strong).
- We suggest that all patients should undergo 3–5 yearly assessment of fibrosis, optimisation of the risk factors for the metabolic syndrome and lifestyle modification (Very low, Moderate).

2.3.6 | Inherited metabolic disorders

- We suggest ongoing MDT input, including a metabolic specialist and hepatologist, ideally in a joint clinic setting (Low, Strong).
- Following liver transplantation for those disorders with only partial correction of the IMD, we recommended continued input from a metabolic specialist (Low, Strong).

2.3.7 | Metabolic dysfunction associated steatotic liver disease

- Young people with metabolic dysfunction associated steatotic liver disease (MASLD) who are known to have advanced fibrosis should be transitioned to adult liver services. In most cases, it will be appropriate for the handover to be to a local secondary care team since MASLD is common and within the scope of the practice of all liver services (Moderate, Strong).
- The enhanced liver fibrosis (ELF) score and/or transient elastography (TE) can be applied at age 16–18 (depending on local policies and agreements) to identify YA with MASLD under low-frequency follow-up in paediatric services who are suitable for continued monitoring in primary care (Low, Moderate).
- YA with MASLD who are discharged to primary care should continue to undergo fibrosis testing using ELF or TE every 2–3 years (Low, Strong).
- Liver biopsy should be considered in young people if advanced fibrosis cannot be confidently excluded by the ELF score or TE. For those under the care of paediatric services, this would be best performed ahead of handover to adult services to help with the planning of long-term care (Low, Moderate).

2.3.8 | Wilson's disease

- YA with WD should be transitioned to an adult liver service with expertise in the management of WD with established multidisciplinary links and expertise (Moderate, Strong).
- The timing of transition for young people with WD will ideally take place at a time of stability and good control (Low, Weak).
- We suggest that mental health concerns and adherence to medications/clinic attendance be supported with the use of the HEADSS tool (Low, Moderate).
- YA with WD should be reviewed at least 6–12 monthly: physical examination, biochemical tests (blood count, liver function tests, urea, creatinine, proteinuria), serum copper and 24-h urinary copper to assess efficacy, overdosage or non-adherence to therapy and adverse events (Low, Strong).

2.4 | Timing and role of liver transplantation

- Early referral is recommended as it allows time for careful assessment and education of the patient and family (Low, Strong).
- Decompensated chronic liver disease (ascites, encephalopathy, spontaneous bacterial peritonitis) merits consideration for referral for liver transplantation (Strong, Strong).
- YA, where possible, should be involved in the decision-making process. We recommend a review of knowledge and understanding of their liver disease, prior adherence and risk-taking behaviours as part of the assessment process (Low, Strong).
- Individualised, YA-specific educational support with the involvement of carer(s)/parent(s) should be undertaken throughout the transplant period (Low, Strong).
- YAs post-LT should be managed in dedicated clinics with MDT support (Low, Strong).

2.5 | Sexual health and fertility

- Pre-pregnancy counselling should be considered for all YA with chronic liver disease, cirrhosis and following liver transplantation to optimise medication regimens, anticipate pregnancy complications and generate delivery plans (Strong, Strong).
- Following liver transplant, pregnancy should be delayed for at least 1 year. This is associated with enhanced maternal and foetal outcomes (Moderate, Strong).
- Immunosuppressive drugs such as azathioprine, cyclosporine, tacrolimus and prednisolone should not be stopped in pregnant women, as there is no increase in congenital malformation (Moderate, Strong).
- Mycophenolate mofetil and sirolimus are teratogenic and should be stopped 12 weeks before conception (Moderate, Strong).

3 | PATIENT SUMMARY

Patient-specific literature is available on the CLDF (Children's Liver Disease Foundation) and the British Liver Trust's websites, respectively.[7,8]

These guidelines have been produced under the auspices of the BSG and the British Association for the Study of the Liver (BASL). They are endorsed by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) and the CLDF. It is aimed at teams of health care professionals that manage YA with liver disease. This patient summary aims to show the key recommendations.

The transition of care from paediatrics to adult services can be a difficult process. YA must juggle the balance of ill health and school/higher education. Maintaining and developing relationships may also be difficult during times of ill health. Financial concerns can be common, and support/guidance is often needed to navigate adult services. Non-adherence is not often deliberate and should be explored by health care professionals in a non-accusatory, blameless fashion. Multi-disciplinary support is required and is integral during the process. Education about the underlying liver disease and medications with the involvement of the carer(s)/parent(s) are important aspects of the transition process. The use of email or text to remind YA of their clinic appointments is recommended. Mental health concerns should be explored routinely, with subsequent access to a dedicated mental health team.

Several liver conditions are covered in this guideline, with specific recommendations made in some conditions. Rare conditions should be managed as part of a multi-disciplinary team. Consideration of liver transplantation should be undertaken early, as standard 'adult' prognostic scores may not be as sensitive in YA. Support and ongoing care within dedicated YA services are needed after a transplant.

4 | MODELS AND PROVISION OF CARE

YAs with complex medical conditions are at high risk for adverse medical, developmental and psychosocial outcomes.[9,10] The period of transition between paediatric and adult health services has a high prevalence of mental health problems, increased rates of non-adherence and is a period of vulnerability that, if conducted poorly, can have significant detrimental effects long term.[10,11] The management of care for YA therefore involves the availability of specialised, transition or YA clinics with multi-disciplinary care input. These clinics often help bridge the difference between paediatric and adult health care models, during which the responsibility of health care shifts from the carer(s)/parent(s) to the YA.[12,13] The process of transition needs to be individualised, meaning a degree of flexibility and age alone should not be the only determinant factor of when a YA should be transferred to adult services.[14,15] A national survey performed in the UK demonstrated that only 61% of secondary and tertiary liver centres had a dedicated liver transition service, with huge variations in the constituents of the multi-disciplinary team.[16]

TABLE 1 Barriers to successful transition of young adults.

Patient factors
• Poor knowledge of their condition
• Negative attitudes towards adult services
• Poor adherence
• Poor knowledge of health care services/structure
• Reluctance to transfer to adult services
Carer(s)/parent(s) factors
• Over-dependence on paediatric providers
• Inadequate sharing of responsibilities with the AYP
• - Inadequate encouragement of independent behaviours
Health care provider factors
• Poor communication between paediatric and adult teams
• Poor coordination of care
• Reluctance of paediatric providers to transfer
• Inexperience in treating childhood disorders by adult provider
• Lack of funding
• Lack of support services that is psychological or social support

Strategies for a successful transition incorporate flexibility, particularly around timing and adopt a person-centred approach.

A number of barriers to a successful transition have been identified and can be categorised according to patient, carer(s)/parent(s) and health care provider factors (Table 1). Patient factors include poor knowledge of their condition, negative attitudes towards adult services, poor adherence, poor knowledge of health care services/structure and reluctance to transfer.[4,16–20] Carer(s)/parent(s) factors include ongoing dependence on paediatric providers, inadequate sharing of responsibilities with the YA and inadequate encouragement of independent behaviours.[4,16,19] Poor communication between health care providers, poor coordination of care, a reluctance of paediatric providers to transfer, inexperience in treating childhood disorders by adult providers, a lack of funding and a lack of support services are the recognised health care provider factors.[4,16,19–21]

4.1 | Models of care

A variety of models have been proposed to help facilitate the transition process, all of which incorporate and highlight the need for joint clinics with paediatric and adult clinical input, planning, continuity of care, flexibility and multi-disciplinary expertise beyond the age of 18 years.[22–24] The UK guidelines on the transition of adolescent or young persons with chronic digestive diseases from paediatric to adult care describe the benefits of the Chronic Care Model (CCM), which helps address these key components.[6,25,26]

4.2 | Young adult roles and self-management

Many YA in the transition period will still be in full-time education. However, they may have missed periods of education due to illness, and attainment may not be as expected for age. The role of the YA changes throughout the transition process, with increasing levels of responsibility. Active participation is encouraged but will progress

at different rates according to the individual. Developing independence, resilience and self-advocacy skills are all important facets that require carer(s)/parental support. 'Avoidant coping', where the individual distracts oneself with social diversion, is a common coping strategy among YA and is associated with disease relapse and inferior outcomes.[27–29] The importance of psychological assessment and support is discussed in Section 5.

A lack of knowledge of one's condition and limited experience in self-care have been identified as risk factors for poor outcomes during transition across several specialties.[19,30–33] It is, therefore, important to develop self-management behaviours that will help YAs to actively participate in their healthcare needs. Self-management behaviours are developed over time and require active participation between the YA, carer(s)/parent(s) and health care providers and affect adherence and outcomes. Shared and supported self-management should be encouraged initially between YA and carer(s)/parent(s) and an individualised, balanced approach to ensure optimal medical adherence and clinical outcomes.[34–37] The use of mobile technology and smart phones to enable self-management should be encouraged, with positive results demonstrated in the management of diabetes.[38–40] The most effective interventions should incorporate technology-enabled self-management feedback loops that connect YA and their health care team using two-way communication, analyse patient-generated health data, provide tailored education and individualise feedback.[41] Certain individuals may benefit from video consultations. Peer-to-peer support and peer networks are additional resources that can benefit a YA.

4.3 | Carer(s)/parent(s) roles

Carer(s)/parent(s) are active, important participants in the transition process and need to be included from the start. Their role will significantly change from primary carer to a more supportive role. They are important advocates for the YA, but their role and involvement also need to be individualised. Poor knowledge of their child's condition has been associated with a low level of parental education.[42] There is often real anxiety among care givers that their child will not be able to manage their own health, which will lead to non-adherence and the worsening of their condition. Anxiety of moving into adult services, thereby leaving their paediatric team, and concerns of the new team having inadequate knowledge of their child's condition/history have been described among carer(s)/parent(s).[43–45] Support and education of carer(s)/parent(s) are also recommended.

4.4 | Young adult clinics and structure

The location of transition clinics should ideally occur within the adult clinical outpatient department, thereby allowing the YA to adapt to the new clinical environment. Community-based clinics can improve geographical and peer group isolation and result in improved graft survival in transplant recipients.[46] The use of psychosocial screening tools in clinics is recommended to personalise care and improve engagement.[47,48] The HEADSS (H—Home, E—Education, A—Activity, D—Drugs, S—Sexuality, S—Suicide/depression) (Table 2) assessment tool has evolved considerably since its introduction but allows the HCP to conduct a structured holistic consultation.[49–51] The THRxEADS (T—Transition, H—Home, Rx—medication and treatment, E—Education and Eating, A—Activities and Affect, D—Drugs, S—Sexuality) mnemonic is an updated tool that may further allow HCPs to better explore the key issues of a YA in a transition clinic episode.[52] A specific pre-university check list is summarised in Table 3.

Assessment of adherence should continue throughout the transition process.[53,54] Objective assessments such as the medication level variability index (MLVI) have been validated in post-transplant patients and may be appropriate in YA on specific medications.[55] The impact of mental health should not be overlooked, with data suggesting mental health disorders, including post-traumatic stress symptoms, are associated with increased rates of non-adherence.[56–59]

4.5 | Readiness for transfer

Readiness for transfer should be frequently assessed throughout the transition period and should/must not be determined solely based on age. The use of 'health passports' is beneficial, especially in individuals with complex health and/or psychosocial need and guidance is available from both paediatric and adult national societies.[6,60–62] The University of North Carolina TR$_x$ANSITION scale is a reliable and tool appropriate to all illnesses that can help identify YAs ready for transfer to adult services.[63] There may be circumstances, however, when a YA is not ready/suitable for transfer. These individuals will therefore need ongoing support and care. The benefit of using 'self-efficacy' questionnaires during the transition process has also demonstrated positive outcomes.[64] A good example of a transition pathway for YA is highlighted in the UK guidelines on the transition of AYP with chronic digestive diseases from paediatric to adult care.[6]

4.5.1 | Recommendations

- We suggest an individualised, multi-disciplinary team approach to YA undergoing transition from paediatric to adult care (Evidence: Moderate; Recommendation: Strong).
- We suggest self-management strategies should be developed with YA and their carer(s)/parent(s) (Moderate, Strong).
- Carer(s)/parent(s) should be encouraged to participate in the transition process (Low, Strong).
- We suggest that the readiness of transfer for YA not be based solely on age (Weak, Strong).

TABLE 2 HEADSS assessment tool. Adapted from Cohen et al (59).

Parameters	Sample questions
H—Home	Who is at home with you? Who at home knows about your condition? Do you have any concerns about your housing?
E—Education, Eating & Education	Does your condition affect you at school? How often do you miss school because of your condition? How does your condition affect your diet and appetite? Does your condition affect how your body looks? In what way? Are you working?
A—Activities and Affect	Does your condition get in the way of participating in activities that your friends do? Do you have any friends or talk to people who have similar health/disability issues? Do you use the internet/social media to connect with other young adults with similar health conditions or learn about your condition? Does your condition affect your sleep? Does your condition affect your sleep? Does your condition make you angry, sad, anxious? Have you ever had suicidal thoughts or tried to hurt yourself? History of past suicide attempts, depression, psychological counselling? History of suicide attempts in family or peers? Suicidal ideation (including significant current and past losses)?
D—Drugs	Do you ever smoke, drink alcohol or use street drugs? Do you ever use alcohol, street drugs to treat your symptoms? What medications do you take and what are they for? What are the doses? Who is in charge of your medications? Do you renew your prescription(s)? What happens if you miss a dose? What do you like and dislike about your medications?
S—Sexuality, Suicide	Are you sexually active? Do you use contraception? Have there been any side effects of your treatment/condition on your sexual health? Have you ever had suicidal thoughts or tried to hurt yourself? History of past suicide attempts, depression, psychological counselling? History of suicide attempts in family or peers? Suicidal ideation (including significant current and past losses)?

5 | SCREENING AND MANAGEMENT OF MENTAL HEALTH DISORDERS

Mental health problems are a major contributor to the global burden of disease, and untreated problems are likely to be very expensive for health services as YA grow into adulthood.[65] Half of all lifetime cases of psychiatric disorders start by age 14, and three quarters by age 24.[66] Common disorders among YA include anxiety and depression, eating disorders and self-harm. Neurodevelopment conditions such as attention-deficit hyperactivity disorder (ADHD) and autism spectrum conditions are also prevalent.[66] The early emergence of psychotic disorders such as schizophrenia can also occur during this developmental period. The limited available evidence indicates an elevated rate of anxiety and depression in YA with chronic liver disease of 17.7%.[10] This is slightly higher than the rate expected in the general population of around 10% but comparable to data in other chronic illness populations.[67–69] Detection, treatment and support for mental health problems are all important parts of the services provided to this age group.

Mental health difficulties and adverse psychosocial circumstances have been associated with poorer health outcomes in young people with liver conditions, including non-adherence to medication and subsequent graft rejection.[56,70] Ideally, prior to clinical review, young people should be asked to complete standardised mental health measures (for example, the Patient Health Questionnaire, PHQ-9 and Generalised Anxiety Disorder-7, GAD-7) to give an indication of current mental health symptomatology and impact. While not essential, the scores on these measures will support the identification of any current mental health needs, including those requiring urgent support, as well as enhance onward referrals for community mental health input. Electronic disclosure of mental health concerns may be easier than during a face-to-face consultation.

With the patient's consent, pre-existing psychosocial information, including any relevant mental health history, should be shared

TABLE 3 Pre-university check list.

What to do if you are thinking of going to university?	Choice of university: Your specialist unit can refer you to the nearest liver/gastro doctor to your university, so don't feel confined to locations close to your current hospital Accommodation: If you are considering student accommodation, you can request a private bathroom for hygiene reasons and a fridge in your room to store medication. Most universities have this option, and your specialist centre can confirm your needs if required
What to do before you start university?	Clinic Appointment: Ensure you have a clinic appointment with your specialist centre prior to starting at university. With plenty of time, a referral can be made to the local liver/gastro adult consultant after this appointment, and useful information included in the clinic letter. Take a copy of this with you to university Deciding on registering with GP at university or not? Pros: √Easier to get medication (especially in an emergency). √Prompt attention to any symptoms. √Your specialist centre can keep your university GP up-to-date with your medical needs. Cons: ×You might not be able to use your regular GP during holidays (although you will still be able to obtain care) ×The university GP will not be as familiar with your background, especially if you have built up a good relationship with your family GP ×Check if your university GP will prescribe all your medications. Take a sufficient supply of medications Prior to going to university, ensure you have a good supply of medications to take with you. You may be able to ask for a longer supply than usual if you explain to your GP Applying for Student Disability Allowance Complete the link below to apply prior to starting university. Part one is for you to complete, then email this to the contact at your specialist centre Contact student support services It is useful for them to know in advance of you starting that you have a medical condition. If any allowances are need in the future (e.g. extensions or extenuating circumstances relating to illness), it is much easier to obtain with prior warning.
What to do at university?	How to contact us Ensure you know how to get in touch with your specialist team while you are at university in case you have any queries. This will most likely be via email, so ensure you know the best contact and you can ask this at your clinic appointments. What to do if you run out of medications • Contact your GP • Contact your specialist hospital pharmacy department if you have their details, or your medical team

with the clinical team. The impact of any pre-existing psychosocial difficulties on condition self-management allows appropriate guidance and signposting within the clinical review. For example, YA struggling to maintain adherence to their medications due to inconsistent daily routines related to low mood and decreased motivation may benefit from temporary support from carer(s)/parent(s) to manage their medication regimen.

For services without embedded mental health professionals, community support may be appropriate and clinicians can signpost to local services (e.g. NHS talking therapies programme [previously known as improving access to psychological therapies, IAPT]) or Community Mental Health Services (CMHT). Many services now accept self-referrals, and details can be found online. Mental health concerns should be pre-empted and taken seriously by clinicians within the routine clinic review, both to engage the YA in discussing their most pertinent concerns and to facilitate appropriate onward referrals.

Alcohol and drug misuse are among the leading risk factors for the burden of disease in the UK.[71] Adolescence is a peak time for the initiation and experimentation of alcohol and drug use, but not all experimentation leads to problematic substance misuse. However, a small number of YA use alcohol or drugs regularly, and a subset of these may progress to have a substance use disorder in young adulthood.[72]

5.1 | Recommendations

- Mental health should be explored routinely in all patients as part of routine clinical practice by a multi-disciplinary team. This can include the use of standardised screening questionnaires, such as the PHQ-9 and GAD-7 (High, Strong).
- Where embedded psychological support is not available, clinicians should familiarise themselves with onward local pathways for mental health support (High, Strong).
- The impact of psychosocial stressors on young people's adherence to medication/clinic attendance and self-management of their condition should be considered (High, Strong).
- Substance use should be explored routinely with patients as part of routine clinical practice. This can include the use of standardised screening questionnaires, such as the AUDIT-C and DAST (High, Strong).

6 | AETIOLOGIES

YA with liver disease diagnosed in childhood can have conditions that are specific paediatric age-onset diseases or diseases that are also seen by adult hepatologists. We discuss common and key aetiologies that require special attention and where they may be differences to adult-onset disease, but this list is not by any means exhaustive. The authors recommend reviewing appropriate paediatric/adult guidelines for more detailed guidance and for aetiologies not covered here.

6.1 | Autoimmune liver disease

In children and YA, autoimmune liver disease (AILD) comprises of autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC). AIH is rare, with a reported incidence of 0.4–3.0/100,000 children.[73,74] Type 1 AIH is characterised by positive antinuclear and anti-smooth muscle antibodies, whereas in type 2 AIH, anti-LKM-1 antibodies are positive. Type 2 more commonly presents in younger children and in an acute fashion including presentation with acute liver failure.[75] Approximately 50% of patients will be cirrhotic at diagnosis.[14] ASC appears to be a unique form of sclerosing cholangitis with serological features of AIH and a cholangiopathy on imaging and is thought to represent an 'inflammatory' phase of primary sclerosing cholangitis (PSC). Patients with ASC are more likely to require liver transplantation.[76]

The commonly used diagnostic tool for AIH in adults, developed by the International Autoimmune Hepatitis Group (IAIHG), is not suitable for the juvenile form.[77] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has published a position paper on autoimmune liver disease summarising the diagnosis and management of juvenile AILD, including a revision of the diagnostic scoring tool to accommodate the differences between children and adults.[78]

AILD responds to immunosuppressive treatment and is an infrequent indication for paediatric liver transplantation. Similar to adult protocols, first-line treatment is with prednisolone 2 mg/kg/day (max 60 mg daily), which is titrated down over a period of 6–8 weeks with at least weekly monitoring of liver function tests. Azathioprine is typically used as a second-line treatment (1 mg/kg/day). Other agents that can be used include mycophenolate mofetil or calcineurin inhibitors. Patients should be managed according to published guidelines.[79] In YA with ASC and PSC, ursodeoxycholic acid (UDCA, 13–15 mg/kg/day) is often prescribed, although data on the positive impact on disease progression is lacking. In addition, there is a paucity of long-term data regarding the burden of immunosuppression on growth and pubertal development. ASC can progress phenotypically to PSC and reassessment with magnetic resonance cholangiopancreatography (MRCP) and liver biopsy and therefore the need for ongoing immunosuppression is recommended.[80]

Response to standard treatment is excellent in AIH, with the majority of patients achieving long-term remission. It is estimated that about 20% of patients will be able to discontinue treatment in type 1 AIH. However, drug withdrawal should not be attempted during puberty, pregnancy or during the transition period and requires a long period (2–3 years) of sustained biochemical and immunological remission.[78] Assessment and monitoring of bone health should be undertaken according to guidelines.[79] Non-adherence to treatment is a particular concern in YA and associated with poor outcomes. Reassessment of the extent and severity of the cholangiopathy with MRCP is recommended every 12–18 months in YA with ASC. Cirrhotic patients should undergo HCC surveillance.

PSC is rare in the paediatric population but has chronic and progressive disease course.[81] YA with PSC with or without inflammatory bowel disease (IBD) should be managed as per published guidelines, with annual surveillance colonoscopies recommended for those with concurrent IBD.[82]

6.1.1 | Recommendations

- Assessment of adherence to treatment using the HEADSS tool should be included in routine clinical setting to avoid relapse of AILD (Low, Strong).
- Cessation of treatment in Type 1 AIH should not be considered during puberty and only after a period of both biochemical and histological remission (High, Strong).
- Patients with ASC should be reassessed (imaging, histology and biochemically) for evolution into PSC and the requirement for ongoing immunosuppression (Low, Strong).
- Bone health screening should be undertaken every 2–3 years (Moderate/Moderate).
- Surveillance with USS for HCC in cirrhotic patients every 6 months (Low, Moderate).

6.2 | Biliary atresia

Biliary atresia is an idiopathic neonatal cholangiopathy characterised by progressive inflammatory obliteration of the intrahepatic and extra-hepatic bile ducts. The presentation is conjugated hyperbilirubinaemia and pale stools within the first 3 months of life.[83,84] The incidence varies from 1 in 5000 to 1 in 20,000 live births worldwide.[85] The commonest type is known as isolated BA and is responsible for the majority of cases.[83] Other types include the syndromic group (typically BA splenic malformation [BASM]) associated with situs inversus (37%) and cardiac abnormalities (45%), cystic BA and cytomegalovirus (CMV) IgM-positive associated BA.[83] A Kasai portoenterostomy (KP), which is ideally performed before the age of 6–8 weeks of life, aims to restore bile flow and alleviate jaundice in approximately 55% of patients.[86] When a KP is unable to salvage the native liver, common complications include jaundice, cholangitis, PHT and/or synthetic failure. These individuals are therefore considered for liver transplantation. BA remains the most common indication for liver transplantation in childhood, with excellent long-term patient and

graft survival. Native liver survival ranges between 23% and 46% at 20 years.[87–89] Serum bilirubin levels >21 μmol/L at the age of 12 years and episodes of cholangitis and variceal bleeding between 12 and 16 years were found to be associated with the need for liver transplantation in adulthood.[84]

Common long-term complications include cholangitis and variceal bleeding. Overall, the development of HCC is rare.[90] YA therefore requires interval liver ultrasound (6–12 monthly) looking for dilated biliary radicles/intra-ductal debris/stones and bile lakes. A change in the baseline findings of a liver ultrasound should lead to axial imaging. Patients with cholangitis should undergo investigation of the patency of the Roux loop by hepatobiliary scintigraphy. An episode of cholangitis should be treated conventionally with antibiotics (intravenous and then oral), according to local microbiology advice.

Patients with evidence of PHT should be managed according to published guidelines.[91] A liver stiffness measurement greater than 24 kPa is a predictor of PHT in older children with BA.[92] Large regenerative nodules from central plate hypertrophy can be noted on USS, but this is rarely associated with malignant transformation.[93] Due to the associated cardiac abnormalities and risk of developing portopulmonary hypertension, yearly transthoracic echocardiograms are recommended in addition to cardiology/cardio-thoracic input.

For those requiring liver transplantation in adulthood, medical and surgical teams should be aware of the anatomical variants associated with BA and the poor sensitivity of prognostic outcome models such as the model for end-stage liver disease (MELD) and the United Kingdom Model for End-Stage Liver Disease (UKELD).[94,95] Neurocognitive outcomes are known to be inferior to that of healthy peers even in those undergoing transplantation at a young age and are likely to affect educational and social outcomes.[96]

6.2.1 | Recommendations

- We suggest YA with BA should be transitioned to an adult liver service with expertise in the management of BA (Low, Strong).
- We suggest that YA with BA be monitored (6–12 monthly) for cholangitis, the complications of cirrhosis and the complications of PHT (Low, Strong).

6.3 | Cholestatic liver diseases

6.3.1 | Progressive familial intrahepatic cholestasis

Progressive familial intrahepatic cholestasis is the umbrella term for a group of disorders with liver disease characterised by severe cholestasis. Based on the molecular pathophysiology and clinical presentation, this was subclassified into three main groups: FIC1 deficiency in PFIC1 (*ATP8B1*), BSEP deficiency in PFIC2 (*ABCB11*) and MDR3 deficiency in PFIC3 (*ABCB4*). The reported incidence (1 in 18,000 live births) is likely to be an under representation as the diagnosis is reliant on the availability of molecular genetic testing.[97] Table 4 summarises the genetic defects, biochemical and clinical manifestations. A small proportion of patients with PFIC do not have variants in these genes.[98] Further evaluation of patients without these variants has led to the recognition of rarer conditions such as TJP2 deficiency (*TJP2*),[99] FXR deficiency (*NR1H4*) and MYO5B deficiency (*MYO5B*).[100] Our understanding continues to develop rapidly, and in those with PFIC without a known variant, it may be that they have not been tested with an up-to-date panel of genes or the aetiology is related to a gene not currently implicated in PFIC.[101] Data from the NAPPED cohorts have demonstrated the utility of serum bile acids in predicting outcomes in PFIC, thereby highlighting their role as targets for treatment.[102]

There is an increasing recognition that individuals who are heterozygotes for variants in the genes seen in PFIC, particularly *ABCB11* and *ABCB4*, can present with milder liver disease phenotypes in adulthood.[103] Although this is considered milder, it still may lead to end-stage liver disease and liver cancer,[104–107] and therefore it is important that when first-degree relatives undergo genetic screening, they are also offered genetic counselling.

FIC1 deficiency

FIC1 (familial intrahepatic cholestasis 1) is encoded by the P-type ATPase gene (*ATP8B1*)[108] and is involved in 'flipping' phosphatidylserine from the outer leaflet to the cytoplasmic membrane inner leaflet, maintaining the distribution and asymmetry of the phospholipid bilayer.[109] Although the true mechanisms of cholestasis in FIC1 deficiency remain unclear, disruption of the membrane may result in

TABLE 4 Genetic defects associated with common conditions and manifestations in adults.

Condition	Gene/protein/chromosome loci/transmission	Defect	Biochemical abnormalities	Risk of HCC	Manifestations
FIC1	ATP8B1/FIC1/18q21-22/AR	ATP-dependent aminophopolipid flippase	GGT—Normal ALT/AST—↑ AFP—Normal	No	• Pruritus • Extra-hepatic symptoms—diarrhoea, pancreatitis, hearing loss
BSEP deficiency	ABCB11/BSEP/2q24/AR	ATP-dependent bile acid bile transporter	GGT—Normal ALT/AST—↑↑↑ AFP—↑	Yes	• Pruritus • No extra-hepatic symptoms
MDR3 deficiency	ABCB4/MDR3/7q21/AR	ATP-dependent phosphatidylcholine floppase	GGT—↑ ALT/AST—↑ AFP—Normal	Yes	• Pruritus • No extra-hepatic symptoms • Choledocholithiasis

a vulnerability to bile acid damage and the impair function of other transporter proteins.[101,109]

FIC1 deficiency presents with cholestasis at a median age of 2 months,[110] typically a normal or low GGT cholestasis with mildly raised transaminases. Although jaundice may be recurrent initially, it becomes permanent in the majority of children.[98] Pruritus and hepatomegaly are almost universally present.[40] Severe disease is associated with progressive hyperbilirubinaemia and PHT in 25% of patients.[110] There is widespread expression of FIC1 in other organs (including small intestine, pancreas and cochlear hair cells), and it is a multi-system disorder associated with short stature, significant diarrhoea, pancreatic insufficiency and sensorineural deafness.[98,110,111]

There is a positive response to UDCA with normalisation of liver tests in 38%.[98] ASBT inhibitors are a therapeutic option to interrupt the enterohepatic circulation of bile acids and have been subjected to clinical trials. In the long-term phase 2 study of marilixibat, the eight patients with PFIC1 did not reduce the serum bile acids or observer-rated pruritus scores from baseline.[112] The phase 3 study of odevixibat demonstrated a reduction in serum bile acids in 17% (none in placebo group) and positive pruritus assessment in 60%, was generally well tolerated,[113] and has received approval for use in PFIC1.[114,115] Surgical interventions that bypass the enterohepatic circulation and reduce the absorption of bile acids include partial external biliary diversion (PEBD), partial internal biliary diversion and ileal bypass, and can result in improvement in liver biochemistry and pruritus.[116] HCC is not described in PFIC1. Liver transplantation in childhood is mainly indicated for severe cholestasis, and from a multi-centre population, 43% required transplantation and transplant-free survival at aged 18 is about 25%.[98,110] Extra-hepatic manifestations tend to continue or even worsen after transplantation, and catch up of stature growth is rare post-childhood transplantation.[98,117] Steatohepatitis can occur in the graft and progress to bridging fibrosis and cirrhosis and is particularly seen in those with chronic diarrhoea.[118] Bile acid resins post-transplant improve intractable diarrhoea and potentially height gain from associated improvement in nutrition.[119]

BSEP deficiency

ATP-dependent bile transport at the canalicular membrane operates against a steep concentration gradient, and BSEP function (encoded by *ABCB11*) is the rate-limiting step and the largest determinant of bile flow from blood to bile.[120,121] BSEP deficiency results in bile acid accumulation and significant hepatocellular damage.

It commonly presents in infancy, at a median age of 2 months, with pruritus, and the majority have hepatomegaly and recurrent or progressive jaundice.[98,110,122] Biochemical abnormalities are characterised by markedly elevated transaminases and serum bile acids, with a low or normal GGT.[110] PHT has also been described. HCC is considered a rare complication in children with liver disease; however, BSEP deficiency was described in 10 children under the age of 5 with HCC.[123] Subsequent reports of larger cohorts with BSEP deficiency have identified HCC or cholangiocarcinoma in 5%–15%.[110,122]

There is growing evidence for a genotype–phenotype correlation in BSEP deficiency. Certain variants in *ABCB11*, for example p.Asp-482Gly, are associated with a more insidious onset, less PHT and no cases of HCC,[110] while individuals with two protein truncating variants more commonly develop HCC.[122] In adulthood, patients with usually milder variants in *ABCB11* can present with ICP and chronic liver disease.[104,105,124]

Medical options for BSEP deficiency are limited, and complete normalisation of liver tests with UDCA is seen in only 31%.[98] ASBT inhibitors have received approval for use in PFIC2.[114] A serum bile acid response was achieved in 40% of patients in the phase 3 study with odevixibat compared to none in the placebo group, and half had a positive pruritus assessment[113,115] Odevixibat is now approved for use in PFIC2. Nasobiliary drainage and surgical biliary diversion are established treatments, which is undertaken at a median age of 2.3 years and is associated with improvements in pruritus and liver biochemistry.[116,125,126] The favourable clinical response is more common in milder genotypes.

Liver transplantation in BSEP deficiency may be indicated in childhood for severe cholestasis, liver failure or HCC. One rare complication post-transplantation is the recurrence of symptoms due to the development of specific allo-reactive antibodies that block the function of the normal BSEP protein.[127] These patients usually respond to increased immunosuppression, but in resistant cases, B-cell depleting therapies may be required.[128]

MDR3 deficiency

ABCB4 encodes MDR3, a protein that 'flops' phosphatidylcholine from the inner cytoplasmic membrane leaflet of the hepatocyte to the outer leaflet, where they are integral to the formation of mixed micelles.[129] Without sufficient phosphatidylcholine, there are free bile acids in bile, which damage the cholangiocyte membrane, resulting in a cholangiopathy.[130] In addition, there is crystallisation of cholesterol and intrahepatic stone formation.[131,132]

The clinical presentation of MDR3 deficiency is usually with cholestasis and a significant elevation in GGT and ALP with the age of onset varying from early childhood to adulthood. The clinical phenotype in adults is varied, ranging from cholelithiasis (low phospolipid-associated cholelithiasis), drug-induced cholestasis, recurrent intrahepatic cholestasis and cholangiopathy. Histology findings are non-specific but include portal inflammation, portal fibrosis, cholestasis and an absence of MDR3 protein expression on immunohistochemistry.[129,133] A greater severity of liver disease is evident in the more severe genotypes.[132,134] Severe presentations of early-onset childhood disease mainly have biallelic variants in *ABCB4*, while heterozygotes can present with a milder phenotype that may resolve during childhood.[135,136] There is a genotype–phenotype correlation in adult-onset disease, which can present with either biallelic variants (which are often of milder severity or variants of unknown significance) or heterozygotes.[104,132]

Treatment with UDCA to reduce the detergent nature of bile can be commenced however there are limitations to its efficacy. Complete normalisation of liver biochemistry is reported in a third

of patients, partial response (jaundice clearance but persistently abnormal biochemistry with progression of fibrosis) in half of patients, while the remainder show no response.[134] There is a genotype-specific response: a complete response is only seen in patients with milder genotypes, and no response in those with protein truncating variants.[134] Treatment with odevixibat has demonstrated an improvement in serum bile acids and pruritus, albeit in a small number of patients.[137] Liver transplantation is a very effective treatment in patients with end-stage liver disease.

6.3.2 | Recommendations

- We suggest individuals with a diagnosis of PFIC and no genetic variant identified on historical testing should consider repeat genetic sequencing with modern technology (Low, Weak).
- First-degree relatives should be offered genetic counselling and clinical review. The age at which the presence of liver disease should be evaluated is unclear, as heterozygotes can present in later life; therefore, longitudinal follow-up is recommended (High, Strong).
- UDCA (10–15 mg/kg) should be trialled. In those with no biochemical response, it can be continued in the absence of side effects (Low, Moderate).
- The use of ASBT inhibitors is recommended (High, Strong).

6.3.3 | Alagille syndrome

Alagille syndrome (ALGS) is an autosomal dominant, multi-system condition that is estimated to affect 1/30,000 to 1/50,000 live births.[138] Individuals with a clinical diagnosis of ALGS have variants in JAG1 in 94%, while a minority have variants in NOTCH2,[139–141] and in the remainder, no variant has been identified. In up to 70% of individuals, no variant can be identified in their parents, and they are considered to have a de novo variant.[142] Where relatives of patients with ALGS have undergone genetic testing and clinical evaluation for ALGS, around 50% with variants have clinical features of ALGS, although these are usually at the milder end of the spectrum.[143] There are a number of specific considerations to consider with genetic counselling in ALGS, including the rate of de novo variants, reduced penetrance, variable expression and somatic/germline mosaicism.[142,144]

Liver involvement is characterised by a paucity of intrahepatic bile ducts, which presents with cholestasis in the majority of patients. The extra-hepatic manifestations include pulmonary and peripheral pulmonary stenosis, vascular anomalies, renal abnormalities, dysmorphic facial features, skeletal features and ocular abnormalities.[145,146] The commonest symptom is pruritus.

Currently, there are no approved drug treatments for ALGS, and the medical options are support, symptom relief and aggressive management of nutritional deficiencies.[147,148] The most frequently prescribed medications for pruritus include UDCA, rifampicin, cholestyramine and naltrexone, and antihistamines can be trialled with varied success. Ongoing clinical trials are investigating the role of ASBT inhibitors in ALGS. In the phase 2b trial, although maralixibat may have reduced pruritus, the primary end-point of ItchoRO reduction was not reached.[149] The majority of the six patients with ALGS who received odevixibat in a phase 2 trial improved their serum bile acids and pruritus assessments.[150]

A small proportion of patients with ALGS and refractory pruritus will proceed to PEBD. Although surgical approaches vary between centres, collaborative data suggest a rapid and sustained relief from pruritus and improvement in cholestasis.[116] Although the majority of these patients undergo surgery in early childhood, there are cases of adolescents aged 16 and 17 who have derived significant benefit from PEBD.[151] Liver transplantation is the most common surgical intervention for ALGS, and from a recent large multi-centre series, 23% underwent liver transplant at a median age of 2.6 years.[152] Long-term outcomes post-liver transplant are excellent, with 71%–100% 1-year survival in more recent series.[153] Adult transplantation for ALGS (age at transplant 30) has comparable patient survival when compared to paediatric transplantation, with 1- and 5-year patient survival rates of 95.5% and 90.9%, respectively.[154]

Estimated transplant-free survival in patients with ALGS at 18.5 years is 24%.[155] At the age of 20, 40% of patients have definite PHT, defined as ascites requiring diuretics, gastro-oesophageal varices or splenomegaly with platelets <150,000/mm^3.[155] The development of HCC in ALGS has not been systemically evaluated, but there are reports of HCC developing in adults with ALGS, and importantly, histological evaluation of non-tumoural tissue does not reveal underlying cirrhosis.[156] It is therefore reasonable to follow standard HCC surveillance guidance in patients with cirrhosis and annual imaging in non-cirrhotic patients.

Intrinsic renal disease is prevalent in ALGS and can first present in adulthood.[157] The most common presentations are renal dysplasia, renal cysts, renal tubular acidosis, vesicoureteral reflux, proteinuria and renovascular hypertension. Renal disease does not improve with liver transplant, and there needs to be close monitoring of renal function post-transplant, with the minimisation of calcineurin inhibitors where possible.[157] A quarter of patients will have a bone fracture by the age of 20, which is usually clustered before the age of 13.[155]

6.3.4 | Recommendations

- We recommend referral for genetic counselling when patients with ALGS are planning a family, or when their family members are undergoing genetic testing (High, Strong).
- We suggest that YA with extra-hepatic (cardiac, pulmonary, renal) manifestations of ALGS should be followed up by the relevant specialists with multi-disciplinary working (Moderate, Strong).
- Consideration of treatment with new therapies that is ASBT inhibitors or inclusion in a clinical trial (High, Strong).

- YA should be managed in specialist centres with early consideration for liver transplantation in those with refractory pruritus and progressive hyperbilirubinaemia (Low, Strong).

6.3.5 | Alpha 1 antitrypsin deficiency

Alpha 1 antitrypsin (A1AT) is a serine protease inhibitor encoded by the *SERPINA1* gene on chromosome 14.[158] Alpha 1 antitrypsin deficiency (AATD) affects 1 in 2000–3500 births, and 95% of cases are homozygous for the Z allele (p.Glu342Lys), which is detected in 1 in 25 North European Caucasians, and 1 in 2000 are homozygotes.[159] Genetic testing is recommended for all first-degree family members of patients with AATD.[160] A1AT is a regulator of the proteolytic effects of neutrophil elastase in the lung[161] and is predominantly synthesised in the hepatocytes. AATD is a multi-system disorder, with toxic gain of function underpinning liver manifestations and loss of physiological function respiratory manifestations.[161] The majority of the Z allele is degraded within the hepatocytes; however, the remainder is retained in the endoplasmic reticulum, where misfolded proteins and polymers are pathogenic.[161] Only a small proportion of A1AT folds effectively and is secreted, resulting in reduced circulating A1AT levels. The pathogenesis of emphysema is a combination of the loss of antiprotease function in the lung, with pro-inflammatory intrapulmonary polymer formation.[162] Other A1AT variants, such as the S allele, have a slower rate of polymer formation so do not develop liver disease, and have higher circulating levels of A1AT so are at lower risk of lung disease.[161]

Clinical liver disease may appear at any age in AATD, and 10% of children with the ZZ genotype develop clinically significant liver disease, with the most common presentation as neonatal cholestasis at 2 months.[163] The majority of cases of neonatal cholestasis will spontaneously resolve; however, approximately 8% of children will develop cirrhosis and PHT.[164] Risk factors for progressive liver disease have not been clearly delineated, but early presentation, prolonged jaundice and more severe histological markers are associated with poorer prognosis.[164,165] AATD predisposes to an early-onset panlobular basal emphysema, which rarely presents in childhood.

There are no specific treatments for liver involvement in AATD, and management should be supportive. Fazirsiran, an RNA interference therapy, demonstrated reduced accumulation of Z-AAT in the liver, reduction in liver enzyme concentrations and fibrosis regression in a small phase 2 study in adults with liver disease.[166] Liver transplantation for AATD accounts for 3.5% of paediatric liver transplantation in the UK, and 17% of those presenting in childhood require a transplant.[161,164] The post-transplant outcomes are excellent, with over 90% 5-year survival for paediatric transplantation[164] and no reported deterioration in lung function.[167]

Longitudinal Swedish data from 200,000 infants screened for AATD demonstrated a gradual reduction in the proportion of ZZ individuals with abnormal liver blood tests through childhood, from over 60% aged 1 to only 8%–17% at age 18.[168] This cohort, which included a subgroup with early-onset liver disease, did not have clinical evidence of liver disease at adolescence. There is, however, a second peak of AATD liver disease in adulthood, with 10% developing cirrhosis and 3% developing PHT,[164] which is generally seen in older never-smokers who have not developed emphysema.[169,160] Of those with AATD liver disease, 15% required liver transplant at a median age of 34–54, which is associated with good outcomes of 80% 5-year survival. Registry data of non-smoking ZZ adults reports cirrhosis as the second most common cause of death (28% of deaths), liver disease as the leading cause of death in those who had cirrhosis and primary liver cancer evident in 38% of those with cirrhosis who died.[169] HCC was detected in 1.3% of adults in a recent systematic review, but only six cases of HCC were included,[164,170] and data from HCC surveillance programmes is not available. Evaluation of explants of patients with AATD who underwent liver transplantation identified HCC in 10%–16%.[170,171]

In the absence of treatments for liver disease, it is key to identify those who develop significant chronic liver disease and manage risk factors associated with progression. The clinical symptoms and biochemical picture of AATD liver disease are often indistinguishable from other aetiologies of cirrhosis.[160] The presence of childhood liver disease,[172] male sex,[164,172,173] elevated BMI[164,173] and metabolic syndrome[164] are risk factors associated with chronic liver disease in adults. The limited data on the effect of alcohol consumption suggests it may not predispose to liver disease[164,173]; however, recommendations are to limit alcohol intake to below the current recommended limits (less than 14 units/week) and stop completely once chronic liver disease has developed.[159] No difference in FEV1 or lung symptoms has been demonstrated between those with and without chronic liver disease.[164]

Regular liver blood tests and monitoring for liver disease at a centre that specialises in AATD are advised.[159] Liver biopsy is the accepted modality for staging chronic liver disease when suspected. Transient elastography with a liver stiffness measurement (LSM) of 8.45 kPa has been proposed for F3 fibrosis (sensitivity 83% and specificity 89%).[174]

AATD lung disease presents in adulthood with an obstructive pattern on spirometry, and accounts for 3.2% of adult lung transplantation in the UK.[161] The most effective treatment is behavioural, with abstinence from smoking and avoiding passive exposure from occupational hazards.[175] Augmentation therapy using pooled plasma with purified A1AT is associated with a reduction in the frequency of respiratory tract infections, but a reduction in decline in lung function has not been demonstrated, and there is no evidence of benefit for the liver component of AATD.[161,176] Recommended baseline investigations in AATD are full lung function tests, including spirometry, lung volumes and gas transfer. Yearly follow-up with spirometry is recommended.

6.3.6 | Recommendations

- We suggest that all patients should undergo yearly liver blood tests and liver ultrasound with regular monitoring for the development of liver disease (Low, Moderate).

- All patients should be educated on the risks of smoking and receive smoking cessation support (High, Strong).
- Patients should undergo yearly pulmonary spirometry (Moderate, Strong).
- We suggest that all patients should undergo 3–5 yearly assessment of fibrosis, optimisation of the risk factors for the metabolic syndrome and lifestyle modification (Very low, Moderate).

6.4 | Inherited metabolic disorders

Inherited metabolic diseases (IMDs) are a heterogeneous and rare group of genetic disorders causing defects in biochemical pathways. Although individually rare, when taken together, they affect approximately 1 in 1000 individuals.[177] Hepatocytes play a key role in several biochemical pathways, including protein synthesis, bile production and the metabolism of proteins, fats and carbohydrates. Disorders of mitochondrial, lysosomal and peroxisomal functions can also present with liver manifestations. Historically, IMDs were considered rare diseases and presenting mainly in infancy or early childhood. However, over the past few years, studies have shown higher incidence rates and older ages at presentation than previously thought.[178] YA with IMDs can often have multi-organ involvement, complex needs and intensive dietary and medical treatments, hence presenting challenges specific to the IMD population. Table 5 summarises the enzymatic defects, clinical features and available management options.

6.4.1 | Recommendations

- We suggest ongoing MDT input, including a metabolic specialist and hepatologist, ideally in a joint clinic setting (Low, Strong).
- Following liver transplantation for those disorders with only partial correction of the IMD, we recommended continued input from a metabolic specialist (Low, Strong).

6.5 | Metabolic dysfunction associated Steatotic liver disease

The term NAFLD (non-alcohol-related fatty liver disease) has been replaced by MASLD, which encompasses patients with hepatic steatosis and have at least one of five cardiometabolic risk factors.[179] It is the commonest cause of chronic liver disease in both children and adults. In addition, paediatric MASLD is associated with higher rates of overall, cancer-, liver- and cardiometabolic-specific mortality compared to the general population.[180] YA with MASLD should be tested for diabetes with HbA1c and an oral glucose tolerance test. Rarer causes of steatosis should also be considered in children and YA, especially in those without clear metabolic risk factors for MASLD and/or if there are additional features such as encephalopathy, jaundice, organomegaly or neuropsychiatric problems (see Table 6).

The worldwide prevalence of MASLD in adults is estimated to be approximately 25%.[181] The estimated prevalence in overweight and obese children and adolescents may be up to 70% and around 7% in those of healthy weight.[182] Data from the UK Avon Longitudinal Study of Parents and Children (ALSPAC) (mean age 24) evaluated the controlled attenuation parameter (CAP) score and TE.[183] The prevalence of suspected steatosis in 3768 individuals with valid CAP scores was 20.7% (defined as ≥248 dB/m), and suspected fibrosis was found in 2.7% of 3600 individuals with valid TE results (defined as ≥7.9 kPa).[183]

Liver biopsy remains the gold standard for the diagnosis of MASLD.[184] Some histological differences have been observed between adult and paediatric MASLD; in children, hepatocyte ballooning and Mallory bodies are less frequent, while portal inflammation is more common.[14,185] The fibrosis stage has been shown to be the most important histological predictor of long-term outcomes and the development of liver-related complications in adults.[186] There is limited longitudinal data on the long-term outcomes in paediatric MASLD, but the full spectrum of disease does occur, with 15% of children having stage 3 fibrosis or greater at diagnosis.[187] MASLD is slowly progressive (advancing by one fibrosis stage every 7–14 years) in the majority of adults and children but can progress more rapidly in around 20% of cases.[188]

6.5.1 | Non-invasive assessment of fibrosis

In adults, several non-invasive tests have been validated for prediction of advanced fibrosis (Kleiner stage ≥3) and are widely used for risk stratification to identify which patients should be referred to or followed up in secondary care.[189,190] The two most validated simple fibrosis scores are the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score (NFS), both of which have high negative predictive value (>90%) for advanced fibrosis (FIB-4 >3.25, NFS >0.675) but are unvalidated in children and adults ≤35 years.[191–194]

The ELF panel (comprising of three direct fibrosis biomarkers: hyaluronic acid, tissue inhibitor of metalloproteinase 1 and amino terminal peptide of procollagen III) performs well at excluding advanced fibrosis in adult MASLD,[189,191] and there was also high accuracy for a cut-off of ≥10.51 for predicting advanced fibrosis in a cohort of 112 children.[195] The National Institute for Health and Care Excellence (NICE) Guideline (2016) on NAFLD: assessment and management recommends using the ELF score with a cut-off of ≥10.51 to identify individuals with MASLD who may have advanced fibrosis and should be referred to a hepatologist.[196] For those with an ELF score of <10.51, it advises retesting every 3 years for adults and every 2 years for children and young people (aged up to 18 years).

Transient elastography (TE) is well validated in adults with MASLD, with increasing data in paediatric patients and YA.[197–199] One study performed in 267 subjects (median age 13 years) highlighted an optimal cut-off for prediction of advanced fibrosis of 8.6 kPa (NPV of 88.1% and 91.3%) in the calibration and validation cohorts.[198]

TABLE 5 Summary of common liver-based inherited metabolic disorders.

IMD category	Defect	Clinical features	Treatment
Disorders of carbohydrate metabolism			
Glycogen storage diseases (GSD)	Type Ia—deficiency of glucose-6-phosphatase Type 1b—deficiency of glucose-6-phosphatase transporter	Hepatomegaly, lactic acidosis, hypoglycaemia, hyperlipidaemia, hypertriglyceridaemia, hyperuricaemia neutropenia, Nephromegaly, short stature Neutropenia and inflammatory bowel disease more common in GSD 1b	Uncooked cornstarch, allopurinol, GCSF Empagliflozin in GSD 1b for neutropenia Liver transplantation Monitoring: • Risk of development of hepatic adenoma • Osteoporosis • Monitoring with liver USS and AFP is recommended
	Type III—deficiency of glycogen debrancher	GSD IIIa—liver and muscle involvement GSD IIIb—liver only Ketosis, hypoglycaemia, hepatomegaly, myopathy, elevated CK	• Uncooked starch • Liver transplantation Monitoring: • Risk of development of hepatic adenoma • Monitoring with liver USS and AFP is recommended
	Type IV—deficiency in glycogen branching	• Hepatomegaly, liver cirrhosis • Cardiomyopathy • Myopathy	• Supportive • Liver transplantation Monitoring: • Echocardiography • Liver USS and AFP
	Type VI (deficiency in phospharylase) and Type IX (deficiency in phospharylase b kinase)	GSD VI—hepatomegaly, ketotic hypoglycaemia GSD IXa—mild hepatic phenotype GSD IXb—mixed hepatic/muscle phenotype GSD IXc—Severe and progressive liver disease	• Supportive • Liver transplantation very rarely
Hereditary fructose intolerance	Deficiency in aldolase B	• Inability to metabolise fructose, sorbitol and sucrose • Gastrointestinal symptoms leading to persistent vomiting, sweating, lethargy, coma and liver failure • Liver disease is rare	Avoidance of fructose, sorbitol and sucrose
Disorders of protein metabolism			
Urea cycle disorders (UCD)	Deficiency in: • N-acetyl-glutamate synthetase(NAGS) • Carbamyl phosphatase synthetase 1 (CPS1) • Ornithine transcarbamylase (OTC) • Arginonosuccinate synthetase (ASS) • Argininosuccinate lyase (ASL) • Arginase (Arg1)	• All UCDs are autosomal recessive except OTC deficiency (X-linked) • NAGS, CPS1, OTC and ASS: hyperammonaemia, encephalopathy, liver dysfunction, seizures and coma • Partial urea cycle deficiencies may go decades before encountering an environmental stress resulting in a hyperammonaemic episode that is dietary protein load, fasting, surgery or pregnancy • Risk of progressive liver disease/cirrhosis in ASL deficiency	Acute episode: • Lowering of ammonia with omission of protein. • Promoting anabolism (sodium benzoate, sodium phenylbutyrate) • Supplementation of arginine ± citrulline • Liver transplantation Monitoring: • Long-term treatment • Ammonia lowering medications • Protein restriction • Emergency regimen Monitoring: • Plasma amino acids and ammonia • Metabolic specialist and dietetic review
	Citrin deficiency	Three age-specific phenotypes: 1. Neonatal intrahepatic cholestasis 2. Failure to thrive and dyslipidaemia in children 3. Recurrent hyperammonaemia and neuropsychiatric symptoms (citrullinaemia type II, CTLN2) Diagnosis confirmed by SLC25A13 genotyping	• Supplement fat-soluble vitamins + lactose-free or formulas containing medium-chain triglyceride (MCT) during periods of liver dysfunction. • In CTLN2 avoidance of precipitants that is alcohol, sugar intake, NSAIDS, surgery. • Low carbohydrate and high protein diet • Liver transplantation has been reported

(Continues)

TABLE 5 (Continued)

IMD category	Defect	Clinical features	Treatment
Hereditary tyrosinaemia type 1 (HT1)	Fumarylacetoacetate hydrolase deficiency	Toxic accumulation of metabolites lead to sever liver dysfunction, renal tubulopathy (hypophosphataemia), porphyria-like syndrome (abdominal pain, myopathy), cardiomyopathy in early life and risk of HCC	• Nitosone 2(2-nitro-4-trifluoromethylbenoyl)-1, 3 cyclohexanedione (NTBC) • Phenylalanine and tyrosine-restricted diet • Phenylalanine and tyrosine amino acid supplements • Liver transplantation if not responsive to NTBC or development of HCC Monitoring • AFP and liver USS/MRI
Organic acidaemias For example Methylmalonic acidaemia (MMA), propionic acidaemia (PA), Maple syrup urine disease (MSUD)		• Accumulation of toxic metabolites causes multi-systemic disease that is basal ganglia injury and complex movement disorders, cardiomyopathy, renal dysfunction, pancreatitis, optic atrophy • MSUD develop neuro-toxicity.	Protein restricted diet. Amino acid supplementation in some • Carnitine supplementation in PA/MMA • Ammonia lowering agents in PA/MMA if required Liver transplantation (best outcomes in MSUD) with milder phenotypes in MMA and PA. Ongoing surveillance for long-term complications of disease in MMA and PA due only partial enzyme replacement Monitoring: • AFP and liver USS • Cardiology surveillance • Renal monitoring • MDT follow-up
Disorders of fatty acid oxidation			
	Defects in mitochondrial fatty acid β oxidation For example MCAD, LCHAD, VLCAD	Symptoms usually occur during catabolic situations. • Hypoketotic hypoglycaemia • Hepatomegaly and liver dysfunction • Cardiomyopathy, myopathy, rhabdomyolysis	Monitoring: • Acute liver failure • Progressive liver dysfunction • Renal function • CK
Mitochondrial disorders			
	Defects in ATP generation via oxidative phosphorylation For example DGUOK, MPV17, POLG, TRMU genes	• Lactic acidosis • Myopathy • Seizures/developmental delay • Acute liver failure often in neonates • Multi-organ involvement	• Supportive • Poor outcomes with liver transplantation in majority
Lysosomal storage disorders (LSD)			
Gaucher's disease	β-glucocerebrosidase deficiency	• Most common LSD • Autosomal recessive • Accumulation of glucocerebroside in monocytes, macrophages (Gaucher cells) in liver, spleen, bone marrow • Three subtypes: 1, visceral without neurological involvement, 2 &3 rapidly progressive and chronic neurological course • Hepatomegaly, focal liver lesions and fibrosis, portal hypertension, HCC	Enzyme replacement therapy Monitoring: • AFP and liver USS
Niemann Pick A and B disease	Lysosomal acid sphingomyelinase deficiency	• Rapid progressive neonatal form, chronic neurovisceral form and chronic visceral form without neurological involvement (hepatosplenomegaly common) • Interstitial lung disease and pulmonary infections common • Mixed lipidaemia • Development of cholestasis, fibrosis and cirrhosis and portal hypertension	Monitoring: • AFP and liver USS • Lipids and cardiovascular disease in NPB

TABLE 5 (Continued)

IMD category	Defect	Clinical features	Treatment
Cholesterol ester storage disorder	Lysosomal acid lipase deficiency (LAL-D)	• Progressive accumulation of cholesterol esters and triglycerides in lysosomes of hepatocytes and macrophages • Later onset characterised by fatty liver, raised aminotransferases. Development of fibrosis and cirrhosis • Increased risk of atherosclerotic vascular disease • Diagnosis made on enzymatic activity measurement and genetic confirmation (autosomal recessive) • High LDL and low HDL	• Enzyme replacement therapy • HSCT reported in some • Liver transplantation reported in some Monitoring: • HDL/LDL • AFP and liver USS

TABLE 6 Conditions associated with hepatic steatosis in children and young adults.

Condition	Associated clinical features
Mitochondrial hepatopathies	Acute liver failure Developmental delay Seizures Myopathy
Disorders of fatty acid metabolism	Acute liver failure Hepatomegaly Cardiomyopathy Myopathy
Urea cycle disorders	Encephalopathy Seizures
Glycogen storage diseases	Hepatomegaly Ketotic hypoglycaemia
Lysosomal acid lipase deficiency	Elevated triglyceride levels
Abetalipoproteinaemia/ Hypobetalipoproteinaemia	Fat malabsorption Psychomotor retardation
Lipodystrophies	Paucity of adipose tissue Hypertriglyceridaemia
Disorders of protein metabolism	Encephalopathy Developmental delay Cardiomyopathy
Wilson's disease	Haemolysis Neuropsychiatric symptoms May be asymptomatic
Cystic fibrosis	Recurrent chest infections Pancreatic insufficiency
Glycogenic hepatopathy	Hepatomegaly Poorly controlled type 1 diabetes
Myopathic disorders	Muscle weakness or pseudohypertrophy

Local pathways should be developed in conjunction with CCGs (clinical commissioning groups) to ensure suitable clinical follow-up for YA with repeat TE or ELF with mild fibrosis every 2–3 years. Significant organisational challenges are anticipated to ensure these repeated scans are undertaken in the current medical and financial climate. YA with moderate fibrosis requires ongoing follow-up with YA services.

6.5.2 | Lifestyle interventions

Promoting healthy eating and regular exercise remain the mainstay of treatment. There is evidence that weight loss is associated with improvements in laboratory abnormalities and liver histology in adults and children with MASLD.[200–202] A proportional weight loss of ≥10% has been associated with improvements in steatosis, resolution of MASLD and regression of fibrosis.[202] There is no clear evidence to support any one specific dietary strategy over another.

YAs often experiment with new experiences and can be influenced by peer pressure. There may be an opportunity, therefore, to influence the establishment of other healthy long-term habits during adolescence that can potentiate MASLD that is avoidance of binge drinking of alcohol, minimal alcohol consumption and non-smoking.

6.5.3 | Medical and surgical therapy

Guidelines from BSPGHAN and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) have concluded that there is insufficient scientific evidence to support the use of any medications or supplements to treat children with MASLD.[203,204] NICE recommends that in children with advanced fibrosis, treatment with vitamin E can be considered in tertiary care settings only, and treatment with vitamin E or pioglitazone can be considered in adults with advanced fibrosis (whether they have diabetes or not) in secondary or tertiary care settings only.[196] Weight gain is a recognised side effect of pioglitazone. The TONIC trial was a large multi-centre RCT that included 173 children and young people (age range 8–17 years) and evaluated metformin and lifestyle counselling or vitamin E and lifestyle counselling against placebo and lifestyle counselling over 96 weeks.[205] In this study, vitamin E did not achieve the primary end-point of a sustained reduction in ALT when compared with placebo but was associated with resolution of steatosis and improvement in hepatocyte ballooning. There are uncertainties around the safety of high-dose vitamin E, as meta-analyses have indicated it may be associated with an increase in all-cause mortality.[206]

Specific candidate pharmacological therapies include the farnesoid X receptor agonist obeticholic acid and GLP-1 analogues, although data are still emerging.[207,208] The daily subcutaneous administration of GLP-1 analogues may limit their use in YA as well as the GI side effects (abdominal pain, diarrhoea and nausea).

Uncomplicated MASLD is not in itself considered to be an indication for bariatric surgery. NSPGHAN and ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) recommend that bariatric surgery may be considered for selected adolescents with a BMI ≥35 kg/m^2, who have non-cirrhotic MASLD and other serious comorbidities (e.g. type 2 diabetes, severe sleep apnoea, idiopathic intracranial hypertension) that are likely to improve with weight loss surgery.[209] NICE also recommends that bariatric surgery may be considered for YA only in exceptional circumstances, and if they have achieved or nearly achieved physiological maturity.[210] A multi-disciplinary team approach is mandated.

6.5.4 | Recommendations

- YA with MASLD who are known to have advanced fibrosis should be transitioned to adult liver services. In most cases, it will be appropriate for the handover to be to a local secondary care team since MASLD is common and within the scope of the practice of all liver services (Moderate, Strong).
- The ELF score and/or TE can be applied at age 16–18 (depending on local policies and agreements) to identify YAs with MASLD under low-frequency follow-up in paediatric services who are suitable for continued monitoring in primary care (Low, Moderate).
- YA with MASLD who are discharged to primary care should continue to undergo fibrosis testing using ELF or TE every 2–3 years (Low, Strong).
- Liver biopsy should be considered in young people if advanced fibrosis cannot be confidently excluded by the ELF score or TE. For those under the care of paediatric services, this would be best performed ahead of handover to adult services to help with the planning of long-term care (Low, Moderate).

6.6 | Wilson's disease

Wilson's disease (WD) is a rare genetic disorder with an estimated incidence of 1 in 30,000.[211] It is characterised by the accumulation of copper predominantly within the liver, brain and corneas that occurs because of impaired biliary excretion of copper. The genetic defect is within the *ATP7B* gene located on chromosome 13, and more than 500 mutations have been identified, with the vast majority that are affected being compound heterozygotes.[212]

Presentation is typically associated with liver disease and/or neuropsychiatric disorders between the ages of 5 and 35 years, with approximately 3% of presentations occurring beyond the 4th decade.[213] It can present with the full spectrum of liver disease, including mild biochemical abnormalities, acute liver failure and cirrhosis and its complications. Haemolysis may be the presenting feature and is commonly associated with severe liver disease.[214] A wide range of neurological (tremor, ataxia, Parkinsonism, dystonia), behavioural (personality change, labile mood, decline in school performance) or psychiatric (paranoia, depression) effects can also occur and may be the first clinical sign.[215,216] The behavioural presentations of WD occurring in YAs are sometimes not recognised as they are thought to be related to adolescence. If WD is not diagnosed and effectively treated, it leads to progressive liver failure and/or irreversible brain damage and will eventually be fatal.

6.6.1 | Diagnosis

Diagnostic features include the presence of Kayser–Fleischer rings (present in 90% of patients with neurological presentations and in 47% with hepatic presentations), low serum ceruloplasmin level (<0.10 g/L), elevated non-ceruloplasmin-bound copper (free copper), elevated 24-h urinary copper excretion (>0.64 μmol [40 μg]), low alkaline phosphatase level and a low alkaline phosphatase to total bilirubin ratio in presentations with acute liver failure and elevated hepatic copper content.[217,218] However, none of these features are pathognomonic in isolation or always present. Liver histology alone is not diagnostic, but typical features include microvesicular and macrovesicular steatosis, glycogenated nuclei and chronic inflammation resembling autoimmune hepatitis. Copper deposition within hepatocytes may be seen but is variable and can occur in other liver diseases associated with impaired bile secretion.[219,220] The combination of Kayser–Fleischer rings and low serum ceruloplasmin level (<0.1 g/L) can be considered diagnostic. BSG-endorsed guidelines on the management of WD have been published recently and provide in-depth information on biochemical parameters and scoring systems.[221]

6.6.2 | Screening in family members

Molecular analysis of the *ATP7B* gene can be performed to help with confirmation of the diagnosis and screening of first-degree relatives. Screening of siblings of WD patients is important because their chance of being a homozygote and subsequently developing the condition is 25%. Offspring of those with WD have a 0.5% chance of being affected, but the likelihood will be greater in consanguineous families. Given that the late onset of WD is recognised, screening of the parents of those affected should also be performed.

6.6.3 | Treatment

YA with WD should be managed with the support of a multi-disciplinary team with input from neurology and neuropsychiatry if appropriate.

Treatment is aimed at removing excess copper by use of chelating agents (penicillamine, trientine) or blockade of intestinal absorption of copper (zinc salts). Penicillamine monotherapy is the first-line treatment for YA and adults, especially those with neurological or psychiatric symptoms. Treatment regimens, timings, dosing and side effects of the common drugs in patients with and without neurological/psychiatric symptoms are summarized by the recent BSG guidelines.[221]

Liver transplantation may be required in cases presenting with acute liver failure with the combination of coagulopathy and encephalopathy, hence fulfilling the UK listing requirements for super urgent liver transplantation. However, those presenting with decompensated cirrhosis in the absence of encephalopathy can often be rescued by treatment with chelators, with improvement occurring over a time period ranging from 1 month to 1 year.[222] Liver transplantation corrects the underlying defect in biliary copper excretion and so long-term medical treatment with copper chelators is not required after LT. However, neuropsychiatric effects may show little improvement or worsen following liver transplantation.

6.6.4 | Monitoring

Adequate monitoring to ensure the efficacy of medical treatment is important. The adequacy of treatment with chelators can be monitored by measuring 24-h urinary copper excretion on treatment, which should be within 3–8 μmol per 24 hs during maintenance treatment. For those treated with zinc, 24-h urinary copper excretion should be <1.6 μmol during treatment. Urinary excretion of zinc can also be measured to check adherence and should be >2 mg in 24 h. Effective treatment should also lead to normalisation of the non-ceruloplasmin-bound copper concentration. Non-ceruloplasmin-bound (free) copper may be a useful parameter to monitor treatment.

BSG, ESPGHAN and EASL have published guidelines regarding the monitoring of patients with WD.[221,223,224]

There are several potential issues that may affect YAs with WD. This may be a time when poor adherence to treatment occurs, and it is important to consider whether any behavioural changes are due to poor control of WD rather than an expected stage of adolescence.[225] Magnetic resonance imaging of the brain to look for characteristic changes could potentially be helpful in identifying the development of neuropsychiatric disease.[226] Clinicians should also be aware of the potential for nutritional deficiencies in iron or zinc and of rarer long-term complications such as Fanconi syndrome or effects of long-term treatment such as Elastosis perforans serpiginosa, which may occur with D-penicillamine use. Genetic counselling may be helpful for young people planning families. Oestrogens may interfere with biliary copper excretion, and increased serum copper and urinary copper excretion have been demonstrated in women taking oestrogen-containing contraceptives and so these are best avoided.[227] Treatment for WD should be continued during pregnancy, but some advocate reducing the dose of chelators to the minimum necessary or 25%–50% of the pre-pregnancy dose, with enhanced monitoring.[228] Women on chelation therapy can breastfeed.

6.6.5 | Recommendations

- YA with WD should be transitioned to an adult liver service with expertise in the management of WD with established multidisciplinary links and expertise (Moderate, Strong).
- The timing of transition for young people with WD will ideally take place at a time of stability and good control (Low, Weak).
- We suggest that adherence to medications and clinic attendance be supported with the use of the HEADSS tool (Low, Moderate).
- YA with WD should be reviewed 6–12 monthly: physical examination, biochemical tests (blood count, liver function tests, urea, creatinine, proteinuria), serum copper and 24-h urinary copper to assess efficacy, overdosage or non-adherence to therapy and adverse events (Low, Strong).

7 | TIMING AND ROLE OF LIVER TRANSPLANTATION

Liver transplantation is a highly effective therapy for patients with acute or chronic liver disease. As children with previously fatal liver disease now survive into adulthood, adult health care providers need to be aware of these diseases and when to refer for transplantation. As this cohort ages, we learn more about their long-term outcomes. However, it remains a rapidly developing field dependent on data from small cohorts from either specialised centres or national/multinational registries.

7.1 | General considerations and when to refer

Prior to referral, there are some simple points to consider: assessment of alternative therapies; patients should be fit enough to survive the procedure; be able to adhere with therapy; and not have significant co-morbidities that significantly affect short- or long-term survival.

Decompensation of chronic liver disease (ascites, encephalopathy, spontaneous bacterial peritonitis) merits consideration for referral for liver transplantation. YAs are usually transplanted for the complications of PHT and portosystemic shunting as opposed to liver failure.[84] Several prognostic scores are available that help clinicians in predicting long-term outcomes and, thereby, the need for liver transplantation. These include the Model for End-stage Liver Disease (MELD), the UKELD and Child–Turcotte–Pugh scores.[229,230] A score that predicts a worse outcome without transplantation at 1 year than survival with transplantation (Child-Pugh ≥8, MELD ≥10 and UKELD ≥49) should lead to referral. However, data from the UK does suggest that UKELD may not be a sensitive descriptor of the severity of liver disease in YAs.[54,84]

Early referral is recommended as it allows time for careful assessment and education of the patient and family. Moreover, transplant listing does not equate to transplantation, with many patients waiting for grafts greater than 6 months. Dedicated guidelines are available for adult liver transplantation.[231] Therefore, this section

will concentrate on points pertinent to diseases of childhood. It is known that developmental delay and the need for special educational support at school are prevalent in children growing up with liver disease, and this should be considered when arranging the liver transplant assessment. For those with severe developmental delay, input from adult safeguarding teams will be required to ensure the YA's needs continue to be met. Formal documentation of the patient's needs in a 'health passport'-type document can be helpful to provide guidance of HCPs involved.

7.2 | Management on the waiting list

YAs, where possible, should be involved in decision-making. We recommend a review of knowledge and understanding of their liver disease, prior adherence and risk-taking behaviours prior to listing. The presence of a psychologist within the YA team has been associated with improved outcomes.[48] Close attention to evolving psychosocial circumstances is recommended at every clinic visit.[10,48] Individualised, one-to-one tailored education packages with carer(s)/parent(s) are recommended.

7.3 | Specific diseases

7.3.1 | BA post-KP

This is the leading indication for liver transplantation among YA.[53,90] The timing of transplantation, however, can be difficult. Cardiac and vascular anomalies can also provide further challenges. Patients should, therefore, undergo detailed assessment with the involvement of experienced respective specialties. Significant splenomegaly with associated hypersplenism is common, and enlargement of the splenic artery with possible aneurysm formation needs to be explored and monitored due to the risk of rupture. Other features noted on axial imaging are intra-abdominal variceal collaterals and spontaneous portosystemic shunts, in particular in those patients with an attenuated portal vein, a common observation in BA.[94] Portal vein thrombosis is rare.[94]

Live transplantation should be considered in patients with persistent jaundice, progressive PHT-related complications (including hepatopulmonary syndrome) and recurrent episodes of cholangitis, in addition to the standard indications. In comparison to adults, the prevalence and severity of covert hepatic encephalopathy in children and young people with liver disease are not well determined.

7.3.2 | Cystic fibrosis

Cystic fibrosis-associated liver disease occurs in around 30% of patients and usually presents before adulthood. Liver failure only accounts for 2.5% of overall CF mortality. Cystic fibrosis is a complex disease to manage due to the multi-system nature of the disease.

The combination of chest disease, sarcopenia, PHT and hepatic dysfunction necessitates a multi-disciplinary clinic approach. The availability of cystic fibrosis transmembrane conductance regulator (CFTR) modulators that is Trikafta or Kaftrio have resulted in improved lung function, nutrition, glycaemic control and quality of life.[232] The impact on liver function and liver disease-related life expectancy remains unclear. The indications for liver transplantation include malnutrition unresponsive to nutritional support, intractable PHT and hepatic dysfunction. Several studies have indicated good initial survival, stabilisation of pulmonary function and nutritional parameters[233] The role and benefit of liver transplantation need to be evaluated with the availability of CFTR modulators.

7.3.3 | Tyrosinaemia type I

Tyrosinaemia type I (HT1) is an autosomal recessive disorder due to a defect of fumaryl acetoacetase (FAA). The clinical phenotype is heterogeneous. Acute liver failure is a common presentation in infants, while older children present with chronic liver disease, rickets, a hypertrophic cardiomyopathy, renal failure or a porphyria-like syndrome. Renal tubular dysfunction and hypophosphatemic rickets can occur at any age.

The long-term outcome of children and YA who have tyrosinaemia type I treated with nitisinone are variable, although a 15-year multi-centre study demonstrated prevention of life-limiting liver disease in patients that commenced treatment <28 days.[234,235] A The mainstay of management is nitisinone, which prevents the accumulation of toxic intermediates (maleylacetoacetate and fumarylacetoacetate) and a phenylalanine- and tyrosine-restricted diet with dried blood spot monitoring of tyrosine and phenylalanine levels. The risk of HCC is markedly reduced in patients treated early (<6 months). α-Fetoprotein monitoring in the clinic should therefore continue with 6 monthly to annual imaging of the liver. Non-adherence to nitisinone can result in an acute porphyric-like crisis with intermittent abdominal pain, muscle weakness and even respiratory failure that could mimic the progressive weakness in Guillain–Barre syndrome. Interruption of treatment leads to inhibition of porphobilinogen synthase by excess succinylacetone. Long-term outcomes of HT1 are associated with neurocognitive and IQ deficits despite treatment; the exact pathophysiology remains unclear.[236]

They require long-term monitoring and follow-up with 6-monthly imaging and AFP for screening of HCC. Liver transplantation is now only indicated for the development of liver failure unresponsive to nitisinone or HCC.[237]

7.3.4 | Liver disease and the Fontan circulation

Congenital cardiac defects that lack two effective ventricles require operations to correct this, leading to the eponymously named Fontan circulation. After a Fontan procedure, the systemic venous return is connected to the pulmonary arteries without

the interposition of an adequate ventricle, and all shunts on the venous, atrial, ventricular and arterial levels are interrupted. The consequence of this operation is chronic systemic venous hypertension and a reduction of cardiac output. In patients with Fontan circulations, chronic venous congestion of the liver associated with chronic hypoxaemia secondary to reduced cardiac output leads to liver cirrhosis.[238]

Fontan-associated liver disease is now well recognised; however, challenges remain around which patients will progress to fibrosis, develop PHT and cirrhosis. Importantly, with the development of cirrhosis comes the risk of HCC in this cohort of patients.[238,239] Patients who may require transplantation for synthetic failure or the development of an HCC ought to have their assessment in a centre with an adult congenital heart disease team.

7.3.5 | Inherited metabolic disorders

Liver transplantation is an established disease-modifying therapy in certain IMD's.[240] In some cases, the correction of the underlying metabolic defect is curative for example OTC deficiency, and in some provides partial correction due to extra-hepatic expression but a milder phenotype for example propionic acidaemia. In the majority of cases, the aim of LT is to prevent end organ damage and hence is recommended early in life. A good medical therapy exists for GSD's; hence, transplantation is only considered if malignancy, poor metabolic control or growth failure are a concern. The risk of hepatic adenomas increases with age, so the majority of liver transplantation in GSD reported are in adults.[240] Although hypoglycaemia and other metabolic parameters are improved with transplant, there are reports of persisting long-term complications, including chronic kidney disease (GSD1a), neutropenia (GSD1b) and cardiac disease (GSD IV).[241] Metabolic specialist input is often required, and if dietary restrictions are continued, metabolic dietetics is also required. The emergency regimen is recommended to be continued in those disorders where only partial correction is achieved, and it is important to reiterate this to the YA. Cardiac and renal surveillance will also be required for life in propionic acidaemia and methylmalonic acidaemia.

7.4 | Outcomes following liver transplantation

Outcomes following LT in YA are excellent, with 1-year and 5-year patient survival rates of >90% and 75%, respectively.[242] However, data does suggest that YAs have an increased rate of graft loss compared to other age groups.[54,243,244] Reasons appear multifactorial, but chronic rejection (CR) has been highlighted as a key aetiology.[53,54] The relationship of CR and poor adherence to medication and clinic attendance is well recognised.[245,246] Poor adherence to medications can exist despite normal liver graft function and is therefore suggested by increased variability in immunosuppression drug levels.[13] YAs post-LT should be managed in dedicated clinics with MDT support with appropriate management strategies, as described in Section 4.4.

7.4.1 | Recommendations

- Early referral is recommended as it allows time for careful assessment and education of the patient and family (Low, Strong).
- Decompensated chronic liver disease (ascites, encephalopathy, spontaneous bacterial peritonitis) merits consideration for referral for liver transplantation (Strong, Strong).
- YA, where possible, should be involved in the decision-making process. We recommend a review of knowledge and understanding of their liver disease, prior adherence and risk-taking behaviours as part of the assessment process (Low, Strong).
- Individualised, YA-specific educational support with the involvement of carer(s)/parent(s) should be undertaken throughout the transplant period (Low, Strong).
- YA post-LT should be managed in dedicated clinics with MDT support (Low, Strong).

8 | SEXUAL HEALTH AND FERTILITY

Improved survival and treatment of children with chronic liver disease, cirrhosis and liver transplant recipients means that the desire for pregnancy is increasing in these groups. In the USA, the prevalence of chronic liver disease in women aged between 15 and 39 years rose from 10.4% in the years 1988–1994 to approximately 25% in the years 2007–2014.[247]

8.1 | Contraception

A key consideration of family planning is the consideration of suitable forms of contraception. Options are listed in Table 7. In stable patients, irrespective of aetiology, all forms of contraception are suitable.

8.2 | Pregnancy

With planning and multi-disciplinary care, excellent outcomes can be anticipated for the majority of patients. Pre-pregnancy counselling allows a proactive approach, which is summarised in Table 8. With some exceptions, such as mycophenolate mofetil, the majority of drugs used in the management of chronic liver disease and following liver transplantation are safe in pregnancy and should not be routinely stopped.

When pregnancy occurs, the normal physiological and hormonal changes of pregnancy can mimic those features seen in chronic liver disease. This includes hyperdynamic circulation, increased cardiac output, increased circulating volume and a fall in peripheral vascular

TABLE 7 Contraception options.

Agent	Chronic liver disease	Cirrhosis	Post-transplant	Effective	Reversibility
Copper IUD	Yes	Yes	Yes	Yes	Yes
Depo MDPA	Yes	Yes	Yes	Yes	Yes
LNG-IUS	Yes	Yes	Yes	Yes	Yes
Progesterone only pill	Yes	Yes	Yes	Yes	Yes
Combined OCP	Yes	Yes[a]	Yes[b]	Yes	Yes
Condoms/barriers	Yes	Yes	Yes	Yes	Yes

Abbreviations: IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; MDPA, medroxyprogesterone acetate; OCP, oral contraceptive pill.

[a]Avoid in decompensated liver disease.

[b]Use alternative in context of patient with impaired graft function.

TABLE 8 Pregnancy counselling topics.

Pre-pregnancy
- Genetic risk to offspring
- Medication review: drug cessation or substitution
- Calculation of prognostic risk scores relating to pregnancy outcome
- Optimise metabolic control and nutritional status in patients with inherited metabolic diseases

Peri-pregnancy
- Assessment of portal hypertension: OGD in second trimester
- Delivery plan

Post-pregnancy
- Risk of medications in breast feeding
- Contraceptive advice
- General advice regarding future liver health and pregnancies

resistance. Clinical findings mirror these physiological changes, such as spider nevi and palmar erythema.

Investigating the pregnant patient should follow the paradigms of standard management. Diagnostic modalities such as ultrasound and magnetic resonance cholangiopancreatography (MRCP) are generally considered safe. Endoscopic procedures such as upper GI endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) can be performed with appropriate discussion and risk–benefit analysis. Similarly, liver biopsy can be performed where the benefit is considered to outweigh the risk.

8.2.1 | Recommendations

- Pre-pregnancy counselling should be considered for all YA with chronic liver disease, cirrhosis and following liver transplantation to optimise medication regimens, anticipate pregnancy complications and generate delivery plans (Strong, Strong).
- Following liver transplant, pregnancy should be delayed for at least 1 year. This is associated with enhanced maternal and foetal outcomes (Moderate, Strong).
- Immunosuppressive drugs such as azathioprine, cyclosporine, tacrolimus and prednisolone should not be stopped in pregnant women, as there is no increase in congenital malformation (Moderate, Strong).
- Mycophenolate mofetil and sirolimus are teratogenic and should be stopped 12 weeks before conception (Moderate, Strong).

9 | AUDIT

- National audit of the provision of transition services for YA among secondary and tertiary liver services.
- The consequence and costs of poor transition in YA that have undergone liver transplantation in childhood.
- Longitudinal assessment of MASLD in YA in primary and secondary care.
- Assessing the consequence and costs of poor transition in YA that have not undergone liver transplantation in childhood.

10 | FUTURE DIRECTIONS AND RESEARCH

- Development of a UK network of liver transition services to facilitate prompt transfer of patients between institutions when moving for higher education/work.
- Understanding of HCC risk in specific aetiologies and the role of surveillance imaging.
- The patient reported experience of barriers to the transition process.
- The patient reported experience of the liver transplant assessment process.
- The incorporation of technology into self-management and its impact on the transition process.
- Review of effective strategies that carer(s)/parent(s) use to support YA's independence.
- Review of the costs of clinic attendance and the costs of medications in the YA population.

AUTHOR CONTRIBUTIONS

Deepak Joshi: Conceptualization; writing – original draft; writing – review and editing. **Jeremy Nayagam:** Conceptualization;

writing – original draft; writing – review and editing. **Lisa Clay:** Conceptualization; writing – original draft; writing – review and editing. **Jenny Yerlett:** Conceptualization; writing – original draft; writing – review and editing. **Lee Claridge:** Conceptualization; writing – original draft; writing – review and editing. **Jemma Day:** Conceptualization; writing – original draft; writing – review and editing. **James Ferguson:** Conceptualization; writing – original draft; writing – review and editing. **Paul Mckie:** Conceptualization; writing – original draft; writing – review and editing. **Roshni Vara:** Conceptualization; writing – original draft; writing – review and editing. **Henry Pargeter:** Conceptualization; writing – original draft; writing – review and editing. **Rachel Lockyer:** Conceptualization; writing – original draft; writing – review and editing. **Rebecca Jones:** Conceptualization; writing – original draft; writing – review and editing. **Michael Heneghan:** Conceptualization; writing – original draft; writing – review and editing. **Marianne Samyn:** Conceptualization; writing – original draft; writing – review and editing.

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AUTHORSHIP

Guarantor of the article: D Joshi.

ORCID

Deepak Joshi https://orcid.org/0000-0001-9547-2809
Jeremy Nayagam https://orcid.org/0000-0002-0344-0218
James Ferguson https://orcid.org/0000-0002-2529-0409
Marianne Samyn https://orcid.org/0000-0003-3837-2304

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